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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a **PROVISIONAL APPLICATION FOR PATENT** under 37 CFR 1.53 (c).

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TITLE OF THE INVENTION (500 characters max)

OPHTHALMIC COMPOSITIONS FOR TREATING OCULAR HYPERTENSION

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ENCLOSED APPLICATION PARTS *(check all that apply)*

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☐ Drawing(s) — *Number of Sheets*
☐ Application Data Sheet. See 37 CFR 1.76
☐ CD(s), Number
☐ Other (specify)

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT *(check one)*

☐ A check or money order is enclosed to cover the filing fees

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The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

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Respectfully submitted,

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TITLE OF THE INVENTION

OPHTHALMIC COMPOSITIONS FOR TREATING OCULAR HYPERTENSION

BACKGROUND OF THE INVENTION

Glaucoma is a degenerative disease of the eye wherein the intraocular pressure is too high to permit normal eye function. As a result, damage may occur to the optic nerve head and result in irreversible loss of visual function. If untreated, glaucoma may eventually lead to blindness. Ocular hypertension, i.e., the condition of elevated intraocular pressure without optic nerve head damage or characteristic glaucomatous visual field defects, is now believed by the majority of ophthalmologists to represent merely the earliest phase in the onset of glaucoma.

Many of the drugs formerly used to treat glaucoma proved unsatisfactory. The early methods of treating glaucoma employed pilocarpine and produced undesirable local effects that made this drug, though valuable, unsatisfactory as a first line drug. More recently, clinicians have noted that many β-adrenergic antagonists are effective in reducing intraocular pressure. While many of these agents are effective for this purpose, there exist some patients with whom this treatment is not effective or not sufficiently effective. Many of these agents also have other characteristics, e.g., membrane stabilizing activity, that become more apparent with increased doses and render them unacceptable for chronic ocular use and can also cause cardiovascular effects.

Although pilocarpine and ß-adrenergic antagonists reduce intraocular pressure, none of these drugs manifests its action by inhibiting the enzyme carbonic anhydrase, and thus they do not take advantage of reducing the contribution to aqueous humor formation made by the carbonic anhydrase pathway.

Agents referred to as carbonic anhydrase inhibitors decrease the formation of aqueous humor by inhibiting the enzyme carbonic anhydrase. While such carbonic anhydrase inhibitors are now used to treat intraocular pressure by systemic and topical routes, current therapies using these agents, particularly those using systemic routes are still not without undesirable effects. Because carbonic anhydrase inhibitors have a profound effect in altering basic physiological processes, the avoidance of a systemic route of administration serves to diminish, if not entirely eliminate, those side effects caused by inhibition of carbonic anhydrase such as metabolic acidosis, vomiting, numbness, tingling, general malaise and the like. Topically effective carbonic anhydrase inhibitors are disclosed in U.S. Patent Nos. 4,386,098; 4,416,890; 4,426,388; 4,668,697; 4,863,922; 4,797,413; 5,378,703, 5,240,923 and 5,153,192.

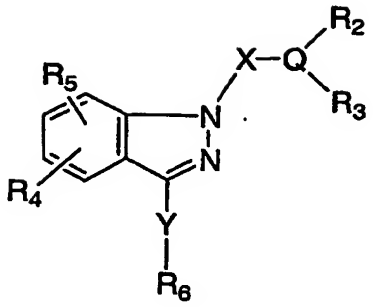
Prostaglandins and prostaglandin derivatives are also known to lower intraocular pressure. U.S. Patent 4,883,819 to Bito describes the use and synthesis of PGAs, PGBs and

PGCs in reducing intraocular pressure. U.S. Patent 4,824,857 to Goh et al. describes the use and synthesis of PGD2 and derivatives thereof in lowering intraocular pressure including derivatives wherein C-10 is replaced with nitrogen. U.S. Patent 5,001,153 to Ueno et al. describes the use and synthesis of 13,14-dihydro-15-keto prostaglandins and prostaglandin derivatives to lower intraocular pressure. U.S. Patent 4,599,353 describes the use of eicosanoids and eicosanoid derivatives including prostaglandins and prostaglandin inhibitors in lowering intraocular pressure. Prostaglandin and prostaglandin derivatives lower intraocular pressure by increasing uveoscleral outflow. This is true for both the F type and A type of Pgs and hence presumably also for the B, C, D, E and J types of prostaglandins and derivatives thereof. A problem with using prostaglandin derivatives to lower intraocular pressure is that these compounds often induce an initial increase in intraocular pressure, can change the color of eye pigmentation and cause proliferation of some tissues surrounding the eye.

As can be seen, there are several current therapies for treating glaucoma and elevated intraocular pressure, but the efficacy and the side effect profiles of these agents are not ideal. Recently potassium channel blockers were found to reduce intraocular pressure in the eye and therefore provide yet one more approach to the treatment of ocular hypertension and the degenerative ocular conditions related thereto. Blockage of potassium channels can diminish fluid secretion, and under some circumstances, increase smooth muscle contraction and would be expected to lower IOP and have neuroprotective effects in the eye. (see US Patent Nos. 5,573,758 and 5,925,342; Moore, et al., Invest. Ophthalmol. Vis. Sci 38, 1997; WO 89/10757, WO94/28900, and WO 96/33719).

SUMMARY OF THE INVENTION

This invention relates to the use of potent potassium channel blockers or a formulation thereof in the treatment of glaucoma and other conditions which are related to elevated intraocular pressure in the eye of a patient. This invention also relates to the use of such compounds to provide a neuroprotective effect to the eye of mammalian species, particularly humans. More particularly this invention relates to the treatment of glaucoma and/or ocular hypertension (elevated intraocular pressure) using novel indazole compounds having the structural formula I:



Formula I

or a pharmaceutically acceptable salt, *in vivo* hydrolysable ester, enantiomer, diastereomer or mixture thereof:
wherein,

R represents hydrogen, or C_{1-6} alkyl;

X represents $-(CHR_7)_p-$, $-(CHR_7)_pCO-$;

Y represents $-CO(CH_2)_n-$, CH_2, or $-CH(OR)-$;

Q represents CR_Y;

R_Y represents H, or C_{1-6} alkyl;

R_w represents H, C_{1-6} alkyl, $-C(O)C_{1-6}$ alkyl, $-C(O)OC_{1-6}$ alkyl, $-SO_2N(R)_2$, $-SO_2C_{1-6}$ alkyl, $-SO_2C_{6-10}$ aryl, NO_2, CN or $-C(O)N(R)_2$;

R_2 represents hydrogen, C_{1-10} alkyl, OH, C_{2-6} alkenyl, C_{1-6} alkylSR, $-(CH_2)_nO(CH_2)_mOR$, $-(CH_2)_nC_{1-6}$ alkoxy, $-(CH_2)_nC_{3-8}$ cycloalkyl, $-(CH_2)_nC_{3-10}$ heterocyclyl, $-N(R)_2$, $-COOR$, or $-(CH_2)_nC_{6-10}$ aryl, said alkyl, heterocyclyl, or aryl optionally substituted with 1-3 groups selected from R^a;

R_3 represents hydrogen, C_{1-10} alkyl, $-(CH_2)_nC_{3-8}$ cycloalkyl, $-(CH_2)_nC_{3-10}$ heterocyclyl, $-(CH_2)_nCOOR$, $-(CH_2)_nC_{6-10}$ aryl, $-(CH_2)_nNHR_8$, $-(CH_2)_nN(R)_2$, $-(CH_2)_nN(R_8)_2$, -

$(CH_2)_nNHCOOR$, $-(CH_2)_nN(R_8)CO_2R$, $-(CH_2)_nN(R_8)COR$, $-(CH_2)_nNHCOR$, $-(CH_2)_nCONH(R_8)$, aryl, $-(CH_2)_nC_{1-6}$ alkoxy, CF_3, $-(CH_2)_nSO_2R$, $-(CH_2)_nSO_2N(R)_2$, $-(CH_2)_nCON(R)_2$, $-(CH_2)_nCONHC(R)_3$, $-(CH_2)_nCONHC(R)_2CO_2R$, $-(CH_2)_nCOR_8$, nitro, cyano or halogen, said alkyl, alkoxy, heterocyclyl, or aryl optionally substituted with 1-3 groups of R^a;

or, R_2 and R_3 taken together with the intervening Q form a 3-10 membered carbocyclic or heterocyclic carbon ring optionally interrupted by 1-2 atoms of O, S, C(O) or NR, and optionally having 1-4 double bonds, and optionally substituted by 1-3 groups selected from R^a;

R_4 and R_5 independently represent hydrogen, C_{1-6} alkoxy, OH, C_{1-6} alkyl, COOR, SO_3H, $-O(CH_2)_nN(R)_2$, $-O(CH_2)_nCO_2R$, $-OPO(OH)_2$, CF_3, OCF_3 $-N(R)_2$, nitro, cyano, C_{1-6} alkylamino, or halogen; and

R_6 represents hydrogen, C_{1-10} alkyl, $-(CH_2)_nC_{6-10}$ aryl, NR_cR_d, $-NR(CH_2)_nC_{6-10}$ aryl, $-N((CH_2)_nC_{6-10}$ aryl$)_2$, $-(CH_2)_nC_{3-10}$ heterocyclyl, $-NR(CH_2)_nC_{3-10}$ heterocyclyl, $-N((CH_2)_nC_{3-10}$ heterocyclyl$)_2$ $(C_{6-10}$ aryl$)O-$, $-(CH_2)_nC_{3-8}$ cycloalkyl, -COOR, $-C(O)CO_2R$, said aryl, heterocyclyl and alkyl optionally substituted with 1-3 groups selected from R^a;

R_c and R_d independently represent H, C1-6 alkyl, C_{2-6} alkenyl, C_{1-6} alkylSR, $-(CH_2)_nO(CH_2)_mOR$, $-(CH_2)_nC_{1-6}$ alkoxy, or $-(CH_2)_nC_{3-8}$ cycloalkyl;

or R_c and R_d taken together with the intervening N atom form a 4-10 membered heterocyclic carbon ring optionally interrupted by 1-2 atoms of O, S, C(O) or NR, and optionally having 1-4 double bonds, and optionally substituted by 1-3 groups selected from R^a;

R_7 represents hydrogen, C_{1-6} alkyl, $-(CH_2)_nCOOR$ or $-(CH_2)_nN(R)_2$,

R_8 represents $-(CH_2)_nC_{3-8}$ cycloalkyl, $-(CH_2)_n$ 3-10 heterocyclyl, C_{1-6} alkoxy or $-(CH_2)_nC_{5-10}$ heteroaryl, $-(CH_2)_nC_{6-10}$ aryl said heterocyclyl, aryl or heteroaryl optionally substituted with 1-3 groups selected from R^a;

R^a represents F, Cl, Br, I, CF_3, $N(R)_2$, NO_2, CN, $-COR_8$, $-CONHR_8$, $-CON(R_8)_2$, $-O(CH_2)_nCOOR$, $-NH(CH_2)_nOR$, -COOR, $-OCF_3$, CF_2CH_2OR, -NHCOR, $-SO_2R$, $-SO_2NR_2$, -SR, $(C_1$-C_6 alkyl$)O-$, $-(CH_2)_nO(CH_2)_mOR$, $-(CH_2)_nC_{1-6}$ alkoxy, (aryl)O-, $-(CH_2)_nOH$, $(C_1$-

C_6 alkyl)$S(O)_m$-, H_2N-C(NH)-, (C_1-C_6 alkyl)C(O)-, (C_1-C_6 alkyl)OC(O)NH-, -(C_1-C_6 alkyl)$NR_w(CH_2)_nC_{3-10}$ heterocyclyl-R_w, -(C_1-C_6 alkyl)$O(CH_2)_nC_{3-10}$ heterocyclyl-R_w, -(C_1-C_6 alkyl)$S(CH_2)_nC_{3-10}$ heterocyclyl-R_w, -(C_1-C_6 alkyl)-C_{3-10} heterocyclyl-R_w, -$(CH_2)_n$-Z^1-$C(=Z^2)N(R)_2$, -(C_{2-6} alkenyl)$NR_w(CH_2)_nC_{3-10}$ heterocyclyl-R_w, -(C_{2-6} alkenyl)$O(CH_2)_nC_{3-10}$ heterocyclyl-R_w, -(C_{2-6} alkenyl)$S(CH_2)_nC_{3-10}$ heterocyclyl-R_w, -(C_{2-6} alkenyl)-C_{3-10} heterocyclyl-R_w, -(C_{2-6} alkenyl)-Z^1-$C(=Z^2)N(R)_2$, -$(CH_2)_nSO_2R$, -$(CH_2)_nSO_3H$, -$(CH_2)_nPO(OR)_2$, C_{3-10}cycloalkyl, C_{6-10} aryl, C_{3-10} heterocyclyl, C_{2-6} alkenyl, and C_1-C_{10} alkyl, said alkyl, alkenyl, alkoxy, heterocyclyl and aryl optionally substituted with 1-3 groups selected from C_1-C_6 alkyl, CN, NO_2, OH, CON(R)2 and COOR;

Z^1 and Z^2 independently represents NR_w, O, CH_2, or S;

m is 0-3;

n is 0-3; and

p is 0-3.

This and other aspects of the invention will be realized upon inspection of the invention as a whole.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to novel potassium channel blockers of Formula I. It also relates to a method for decreasing elevated intraocular pressure or treating glaucoma by administration, preferably topical or intra-camaral administration, of a composition containing a potassium channel blocker of Formula I described hereinabove and a pharmaceutically acceptable carrier.

One embodiment of this invention is realized when p is 1-3.

Another embodiment of this invention is realized when Y is -$CO(CH_2)_n$ and all other variables are as originally described. A subembodiment of this invention is realized when n is 0.

Another embodiment of this invention is realized when Y is CH(OR) and all other variables are as originally described.

In another embodiment R_w is selected from H, C_{1-6} alkyl, -$C(O)C_{1-6}$ alkyl and -C(O)N(R)2 and all other variables are as originally described..

In another embodiment X is $-(CHR_7)_p-$, p is 1-3 and all other variables are as originally described.

In another embodiment X is $-(CHR_7)_pCO-$, p is 1-3 and all other variables are as originally described.

Still another embodiment of this invention is realized when R_6 is $(CH_2)_nC_{6-10}$ aryl, $(CH_2)_nC_{3-10}$ heterocyclyl, NR_cR_d or $(CH_2)_nC_{3-8}$ cycloalkyl, said aryl, heterocyclyl and cycloalkyl optionally substituted with 1 to 3 groups of R^a, and all other variables are as originally described.

Yet another embodiment of this invention is realized when R_6 is $(CH_2)_nC_{6-10}$ aryl, NR_cR_d, or $(CH_2)_nC_{3-10}$ heterocyclyl, said aryl, and heterocyclyl optionally substituted with 1 to 3 groups of R^a, and all other variables are as originally described.

Yet another embodiment of this invention is realized when R_7 is hydrogen or C_{1-6} alkyl, and all other variables are as originally described.

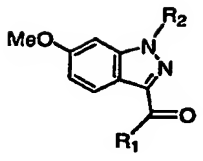
Yet another embodiment of this invention is realized when Y is $-CO(CH_2)_n$, and n is 0.

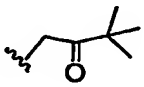
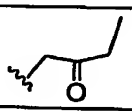
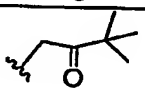
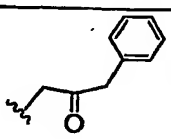
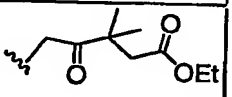
Still another embodiment of this invention is realized when Y is $-CO(CH_2)_n$, R_2 is C_{1-10} alkyl or C_{1-6} alkylOH and R_3 is C_{1-10} alkyl or $(CH_2)_nC_{3-10}$ heterocyclyl, said heterocyclyl and alkyl optionally substituted with 1 to 3 groups of R^a. A subembodiment of this invention is realized when n is 0.

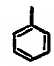
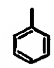
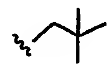
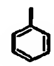
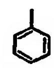
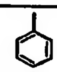
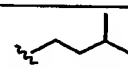
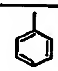
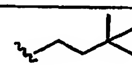
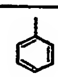
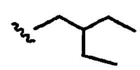
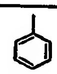
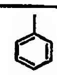
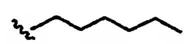
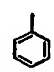
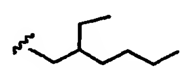
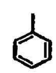
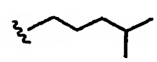
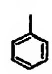
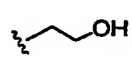
Another embodiment of the instant invention is realized when R^a is selected from F, Cl, Br, I, CF_3, $N(R)_2$, NO_2, CN, $-CONHR_8$, $-CON(R_8)_2$, $-O(CH_2)_nCOOR$, $-NH(CH_2)_nOR$, -COOR, $-OCF_3$, -NHCOR, $-SO_2R$, $-SO_2NR_2$, -SR, $(C_1-C_6$ alkyl)O-, $-(CH_2)_nO(CH_2)_mOR$, $-(CH_2)_nC_{1-6}$ alkoxy, (aryl)O-, -OH, $(C_1-C_6$ alkyl)$S(O)_m-$, $H_2N-C(NH)-$, $(C_1-C_6$ alkyl)C(O)-, $(C_1-C_6$ alkyl)OC(O)NH-, $-(C_1-C_6$ alkyl)$NR_w(CH_2)_nC_{3-10}$ heterocyclyl-R_w, $-(CH_2)_n-Z^1-C(=Z^2)N(R)_2$, $-(C_{2-6}$ alkenyl)$NR_w(CH_2)_nC_{3-10}$ heterocyclyl-R_w,$-(C_{2-6}$ alkenyl)$-Z^1-C(=Z^2)N(R)_2$,$-(CH_2)_nSO_2R$, $-(CH_2)_nSO_3H$, $-(CH_2)_nPO(OR)_2$, C_{2-6} alkenyl, and C_1-C_{10} alkyl, said alkyl and alkenyl, optionally substituted with 1-3 groups selected from C_1-C_6 alkyl, and COOR;

Examples of compounds to be used in this invention are found in Tables 1 and 2 :

Table 1



R1	R2
	
	
	
	
	
	

R1	R2
	
	
	
	
	
	
	
	
	
	
	
	

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	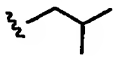
	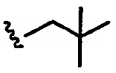
	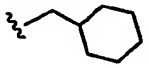
	
	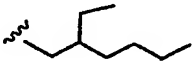

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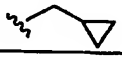
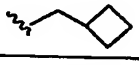
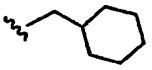
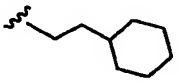
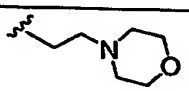
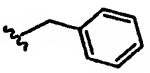
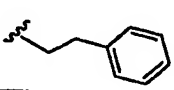
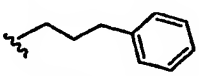
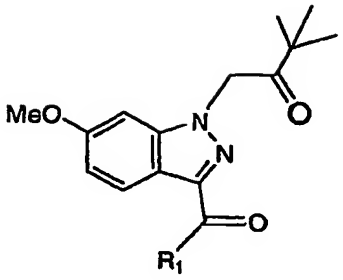
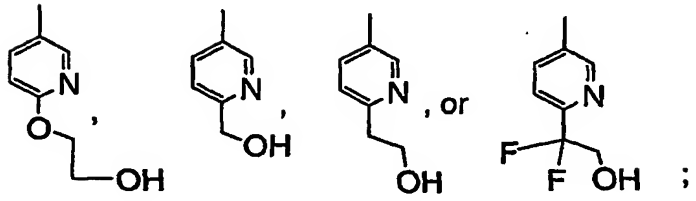
	
	
	
	
	
	
	
	

Table 2



wherein R_1 is



;

or a pharmaceutically acceptable salt, *in vivo* hydrolysable ester, enantiomer, diastereomer or mixture thereof.

The invention is described herein in detail using the terms defined below unless otherwise specified.

The compounds of the present invention may have asymmetric centers, chiral axes and chiral planes, and occur as racemates, racemic mixtures, and as individual diastereomers, with all possible isomers, including optical isomers, being included in the present invention. (See E.L. Eliel and S.H. Wilen *Stereochemistry of Carbon Compounds* (John Wiley and Sons, New York 1994), in particular pages 1119-1190)

When any variable (e.g. aryl, heterocycle, R^1, R^6 etc.) occurs more than one time in any constituent, its definition on each occurrence is independent at every other occurrence. Also, combinations of substituents/or variables are permissible only if such combinations result in stable compounds.

The term "alkyl" refers to a monovalent alkane (hydrocarbon) derived radical containing from 1 to 10 carbon atoms unless otherwise defined. It may be straight, branched or cyclic. Preferred alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, t-butyl, cyclopropyl cyclopentyl and cyclohexyl. When the alkyl group is said to be substituted with an alkyl group, this is used interchangeably with "branched alkyl group".

Cycloalkyl is a specie of alkyl containing from 3 to 15 carbon atoms, unless otherwise defined, without alternating or resonating double bonds between carbon atoms. It may contain from 1 to 4 rings, which are fused. Examples of such cycloalkyl elements include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

Alkenyl is C_2-C_6 alkenyl.

Alkoxy refers to an alkyl group of indicated number of carbon atoms attached through an oxygen bridge, with the alkyl group optionally substituted as described herein. Said groups are those groups of the designated length in either a straight or branched configuration and if two or more carbon atoms in length, they may include a double or a triple bond. Exemplary of such alkoxy groups are methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tertiary butoxy, pentoxy, isopentoxy, hexoxy, isohexoxy allyloxy, propargyloxy, and the like.

Halogen (halo) refers to chlorine, fluorine, iodine or bromine.

Aryl refers to aromatic rings e.g., phenyl, substituted phenyl and the like, as well as rings which are fused, e.g., naphthyl, phenanthrenyl and the like. An aryl group thus contains at least one ring having at least 6 atoms, with up to five such rings being present, containing up to 22 atoms therein, with alternating (resonating) double bonds between adjacent carbon atoms or suitable heteroatoms. Examples of aryl groups are phenyl, naphthyl, tetrahydronaphthyl, indanyl, biphenyl, phenanthryl, anthryl or acenaphthyl and phenanthrenyl, preferably phenyl, naphthyl or phenanthrenyl. Aryl groups may likewise be substituted as defined. Preferred substituted aryls include phenyl and naphthyl.

The term heterocyclyl or heterocyclic, as used herein, represents a stable 3- to 7-membered monocyclic or stable 8- to 11-membered bicyclic heterocyclic ring which is either saturated or unsaturated, and which consists of carbon atoms and from one to four heteroatoms selected from the group consisting of N, O, and S, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. A fused heterocyclic ring system may include carbocyclic rings and need include only one heterocyclic ring. The term heterocycle or heterocyclic includes heteroaryl moieties. Examples of such heterocyclic elements include, but are not limited to, azepinyl, benzimidazolyl, benzisoxazolyl, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, cinnolinyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, dihydropyrrolyl, 1,3-dioxolanyl, furyl, imidazolidinyl, imidazolinyl, imidazolyl, indolinyl, indolyl, isochromanyl, isoindolinyl, isoquinolinyl, isothiazolidinyl, isothiazolyl, isothiazolidinyl, morpholinyl, naphthyridinyl,

oxadiazolyl, 2-oxoazepinyl, oxazolyl, 2-oxopiperazinyl, 2-oxopiperdinyl, 2-oxopyrrolidinyl, piperidyl, piperazinyl, pyridyl, pyrazinyl, pyrazolidinyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrrolidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrahydrofuryl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiazolyl, thiazolinyl, thienofuryl, thienothienyl, and thienyl. Preferably, heterocycle is selected from 2-azepinonyl, benzimidazolyl, 2-diazapinonyl, dihydroimidazolyl, dihydropyrrolyl, imidazolyl, 2-imidazolidinonyl, indolyl, isoquinolinyl, morpholinyl, piperidyl, piperazinyl, pyridyl, pyrrolidinyl, 2-piperidinonyl, 2-pyrimidinonyl, 2-pyrollidinonyl, quinolinyl, tetrahydrofuryl, tetrahydroisoquinolinyl, and thienyl.

The term "heteroatom" means O, S or N, selected on an independent basis.

The term "heteroaryl" refers to a monocyclic aromatic hydrocarbon group having 5 or 6 ring atoms, or a bicyclic aromatic group having 8 to 10 atoms, containing at least one heteroatom, O, S or N, in which a carbon or nitrogen atom is the point of attachment, and in which one or two additional carbon atoms is optionally replaced by a heteroatom selected from O or S, and in which from 1 to 3 additional carbon atoms are optionally replaced by nitrogen heteroatoms, said heteroaryl group being optionally substituted as described herein. Examples of such heterocyclic elements include, but are not limited to, benzimidazolyl, benzisoxazolyl, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, cinnolinyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, furyl, imidazolyl, indolinyl, indolyl, isochromanyl, isoindolinyl, isoquinolinyl, isothiazolyl, naphthyridinyl, oxadiazolyl, pyridyl, pyrazinyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, thiazolyl, thienofuryl, thienothienyl, thienyl and triazolyl. Additional nitrogen atoms may be present together with the first nitrogen and oxygen or sulfur, giving, e.g., thiadiazole.

This invention is also concerned with a method of treating ocular hypertension or glaucoma by administering to a patient in need thereof one of the compounds of formula I in combination with a β-adrenergic blocking agent such as timolol, a parasympathomimetic agent such as pilocarpine, carbonic anhydrase inhibitor such as dorzolamide, acetazolamide, metazolamide or brinzolamide, a prostaglandin such as latanoprost, rescula, S1033 or a prostaglandin derivative such as a hypotensive lipid derived from PGF2α prostaglandins. An example of a hypotensive lipid (the carboxylic acid group on the α-chain link of the basic prostaglandin structure is replaced with electrochemically neutral substituents) is that in which

the carboxylic acid group is replaced with a C_{1-6} alkoxy group such as OCH_3 (PGF_{2a} 1-OCH_3), or a hydroxy group (PGF_{2a} 1-OH).

Preferred potassium channel blockers are calcium activated potassium channel blockers. More preferred potassium channel blockers are high conductance, calcium activated potassium (Maxi-K) channel blockers. Maxi-K channels are a family of ion channels that are prevalent in neuronal, smooth muscle and epithelial tissues and which are gated by membrane potential and intracellular Ca^{2+}.

Intraocular pressure (IOP) is controlled by aqueous humor dynamics. Aqueous humor is produced at the level of the non-pigmented ciliary epithelium and is cleared primarily via outflow through the trabecular meshwork. Aqueous humor inflow is controlled by ion transport processes. It is thought that maxi-K channels in non-pigmented ciliary epithelial cells indirectly control chloride secretion by two mechanisms; these channels maintain a hyperpolarized membrane potential (interior negative) which provides a driving force for chloride efflux from the cell, and they also provide a counter ion (K^+) for chloride ion movement. Water moves passively with KCl allowing production of aqueous humor. Inhibition of maxi-K channels in this tissue would diminish inflow. Maxi-K channels have also been shown to control the contractility of certain smooth muscle tissues, and, in some cases, channel blockers can contract quiescent muscle, or increase the myogenic activity of spontaneously active tissue. Contraction of ciliary muscle would open the trabecular meshwork and stimulate aqueous humor outflow, as occurs with pilocarpine. Therefore maxi-K channels could profoundly influence aqueous humor dynamics in several ways; blocking this channel would decrease IOP by affecting inflow or outflow processes or by a combination of affecting both inflow/outflow processes.

The present invention is based upon the finding that maxi-K channels, if blocked, inhibit aqueous humor production by inhibiting net solute and H_2O efflux and therefore lower IOP. This finding suggests that maxi-K channel blockers are useful for treating other ophthamological dysfunctions such as macular edema and macular degeneration. It is known that lowering IOP promotes blood flow to the retina and optic nerve. Accordingly, the compounds of this invention are useful for treating macular edema and/or macular degeneration.

Macular edema is swelling within the retina within the critically important central visual zone at the posterior pole of the eye. An accumulation of fluid within the retina tends to detach the neural elements from one another and from their local blood supply, creating a dormancy of visual function in the area.

Glaucoma is characterized by progressive atrophy of the optic nerve and is frequently associated with elevated intraocular pressure (IOP). It is possible to treat glaucoma,

however, without necessarily affecting IOP by using drugs that impart a neuroprotective effect. See Arch. Ophthalmol. Vol. 112, Jan 1994, pp. 37-44; Investigative Ophthamol. & Visual Science, 32, 5, April 1991, pp. 1593-99. It is believed that maxi-K channel blockers which lower IOP are useful for providing a neuroprotective effect. They are also believed to be effective for increasing retinal and optic nerve head blood velocity and increasing retinal and optic nerve oxygen by lowering IOP, which when coupled together benefits optic nerve health. As a result, this invention further relates to a method for increasing retinal and optic nerve head blood velocity, increasing retinal and optic nerve oxygen tension as well as providing a neuroprotective effect or a combination thereof.

As indicated above, potassium channel antagonists are useful for a number of physiological disorders in mammals, including humans. Ion channels, including potassium channels, are found in all mammalian cells and are involved in the modulation of various physiological processes and normal cellular homeostasis. Potassium ions generally control the resting membrane potential, and the efflux of potassium ions causes repolarization of the plasma membrane after cell depolarization. Potassium channel antagonists prevent repolarization and enable the cell to stay in the depolarized, excited state.

There are a number of different potassium channel subtypes. Physiologically, one of the most important potassium channel subtypes is the Maxi-K channel which is present in neuronal tissue, smooth muscle and epithelial tissue. Intracellular calcium concentration (Ca^{2+}_i) and membrane potential gate these channels. For example, Maxi-K channels are opened to enable efflux of potassium ions by an increase in the intracellular Ca^{2+} concentration or by membrane depolarization (change in potential). Elevation of intracellular calcium concentration is required for neurotransmitter release. Modulation of Maxi-K channel activity therefore affects transmitter release from the nerve terminal by controlling membrane potential, which in turn affects the influx of extracellular Ca^{2+} through voltage-gated calcium channels. The compounds of the present invention are therefore useful in the treatment of neurological disorders in which neurotransmitter release is impaired.

A number of marketed drugs function as potassium channel antagonists. The most important of these include the compounds Glyburide, Glipizide and Tolbutamide. These potassium channel antagonists are useful as antidiabetic agents. The compounds of this invention may be combined with one or more of these compounds to treat diabetes.

Potassium channel antagonists are also utilized as Class 3 antiarrhythmic agents and to treat acute infarctions in humans. A number of naturally occuring toxins are known to block potassium channels including Apamin, Iberiotoxin, Charybdotoxin, Noxiustoxin, Kaliotoxin, Dendrotoxin(s), mast cell degranuating (MCD) peptide, and β-Bungarotoxin (β-

BTX). The compounds of this invention may be combined with one or more of these compounds to treat arrhythmias.

Depression is related to a decrease in neurotransmitter release. Current treatments of depression include blockers of neurotransmitter uptake, and inhibitors of enzymes involved in neurotransmitter degradation which act to prolong the lifetime of neurotransmitters.

Alzheimer's disease is also characterized by a diminished neurotransmitter release. Alzheimer's disease is a neurodegenerative disease of the brain leading to severely impaired cognition and functionality. This disease leads to progressive regression of memory and learned functions. Alzheimer's disease is a complex disease that affects cholinergic neurons, as well as serotonergic, noradrenergic and other central neurotransmitter systems. Manifestations of Alzheimer's disease extend beyond memory loss and include personality changes, neuromuscular changes, seizures, and occasionally psychotic features.

Alzheimer's disease is the most common type of dementia in the United States. Some estimates suggest that up to 47% of those older than 85 years have Alzheimer's disease. Since the average age of the population is on the increase, the frequency of Alzheimer's disease is increasing and requires urgent attention. Alzheimer's is a difficult medical problem because there are presently no adequate methods available for its prevention or treatment.

Three classes of drugs are being investigated for the treatment of Alzheimer's disease. The first class consists of compounds that augment acetylcholine neurotransmitter function. Currently, cholinergic potentiators such as the anticholinesterase drugs are being used in the treatment of Alzheimer's disease. In particular, physostigmine (eserine), an inhibitor of acetylcholinesterase, has been used in its treatment. The administration of physostigmine has the drawback of being considerably limited by its short half-life of effect, poor oral bioavailability, and severe dose-limiting side-effects, particularly towards the digestive system. Tacrine (tetrahydroaminocridine) is another cholinesterase inhibitor that has been employed; however, this compound may cause hepatotoxicity.

A second class of drugs that are being investigated for the treatment of Alzheimer's disease is nootropics that affect neuron metabolism with little effect elsewhere. These drugs improve nerve cell function by increasing neuron metabolic activity. Piracetam is a nootropic that may be useful in combination with acetylcholine precursors and may benefit Alzheimer's patients who retain some quantity of functional acetylcholine release in neurons. Oxiracetam is another related drug that has been investigated for Alzheimer treatment.

A third class of drugs is those drugs that affect brain vasculature. A mixture of ergoloid mesylates is used for the treatment of dementia. Ergoloid mesylates decrease vascular resistance and thereby increase cerebral blood flow. Also employed are calcium channel

blocking drugs including Nimodipine which is a selective calcium channel blocker that affects primarily brain vasculature.

Other miscellaneous drugs are targeted to modify other defects found in Alzheimer's disease. Selegiline, a monoamine oxidase B inhibitor which increases brain dopamine and norepinephrine has reportedly caused mild improvement in some Alzheimer's patients. Aluminum chelating agents have been of interest to those who believe Alzheimer's disease is due to aluminum toxicity. Drugs that affect behavior, including neuroleptics, and anxiolytics have been employed. Side effects of neuroleptics range from drowsiness and anti cholinergic effects to extrapyramidal side effects; other side effects of these drugs include seizures, inappropriate secretion of antidiuretic hormone, jaundice, weight gain and increased confusion. Anxiolytics, which are mild tranquilizers, are less effective than neuroleptics, but also have milder side effects. Use of these behavior-affecting drugs, however, remains controversial. The present invention is related to novel compounds which are useful as potassium channel antagonists. It is believed that certain diseases such as depression, memory disorders and Alzheimers disease are the result of an impairment in neurotransmitter release. The potassium channel antagonists of the present invention may therefore be utilized as cell excitants which should stimulate an unspecific release of neurotransmitters such as acetylcholine, serotonin and dopamine. Enhanced neurotransmitter release should reverse the symptoms associated with depression and Alzheimers disease.

The compounds within the scope of the present invention exhibit potassium channel antagonist activity and thus are useful in disorders associated with potassium channel malfunction. A number of cognitive disorders such as Alzheimer's Disease, memory loss or depression may benefit from enhanced release of neurotransmitters such as serotonin, dopamine or acetylcholine and the like. Blockage of Maxi-K channels maintains cellular depolarization and therefore enhances secretion of these vital neurotransmitters.

The compounds of this invention may be combined with anticholinesterase drugs such as physostigmine (eserine) and Tacrine (tetrahydroaminocridine), nootropics such as Piracetam, Oxiracetam, ergoloid mesylates, selective calcium channel blockers such as Nimodipine, or monoamine oxidase B inhibitors such as Selegiline, in the treatment of Alzheimer's disease. The compounds of this invention may also be combined with Apamin, Iberiotoxin, Charybdotoxin, Noxiustoxin, Kaliotoxin, Dendrotoxin(s), mast cell degranuating (MCD) peptide, β-Bungarotoxin (β-BTX) or a combination thereof in treating arrythmias. The compounds of this invention may further be combined with Glyburide, Glipizide, Tolbutamide or a combination thereof to treat diabetes.

The herein examples illustrate but do not limit the claimed invention. Each of the claimed compounds are potassium channel antagonists and are thus useful in the decribed neurological disorders in which it is desirable to maintain the cell in a depolarized state to achieve maximal neurotransmitter release. The compounds produced in the present invention are readily combined with suitable and known pharmaceutically acceptable excipients to produce compositions which may be administered to mammals, including humans, to achieve effective potassium channel blockage.

For use in medicine, the salts of the compounds of formula I will be pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their pharmaceutically acceptable salts. When the compound of the present invention is acidic, suitable "pharmaceutically acceptable salts" refers to salts prepared form pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as arginine, betaine caffeine, choline, N,N^1-dibenzylethylenediamine, diethylamin, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine tripropylamine, tromethamine and the like.

When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric and tartaric acids.

The preparation of the pharmaceutically acceptable salts described above and other typical pharmaceutically acceptable salts is more fully described by Berg *et al.*, "Pharmaceutical Salts," *J. Pharm. Sci.*, 1977:66:1-19.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specific amounts, as well as any product which

results, directly or indirectly, from combination of the specific ingredients in the specified amounts.

When a compound according to this invention is administered into a human subject, the daily dosage will normally be determined by the prescribing physician with the dosage generally varying according to the age, weight, sex and response of the individual patient, as well as the severity of the patient's symptoms.

The maxi-K channel blockers used can be administered in a therapeutically effective amount intravaneously, subcutaneously, topically, transdermally, parenterally or any other method known to those skilled in the art.

Ophthalmic pharmaceutical compositions are preferably adapted for topical administration to the eye in the form of solutions, suspensions, ointments, creams or as a solid insert. Ophthalmic formulations of this compound may contain from 0.01 ppm to 1% and especially 0.1 ppm to 1% of medicament. Higher dosages as, for example, about 10% or lower dosages can be employed provided the dose is effective in reducing intraocular pressure, treating glaucoma, increasing blood flow velocity or oxygen tension. For a single dose, from between 0.01 to 5000 ng, preferably 0.1 to 500 ng, and especially 1to 100 ng of the compound can be applied to the human eye.

The pharmaceutical preparation which contains the compound may be conveniently admixed with a non-toxic pharmaceutical organic carrier, or with a non-toxic pharmaceutical inorganic carrier. Typical of pharmaceutically acceptable carriers are, for example, water, mixtures of water and water-miscible solvents such as lower alkanols or aralkanols, vegetable oils, polyalkylene glycols, petroleum based jelly, ethyl cellulose, ethyl oleate, carboxymethyl-cellulose, polyvinylpyrrolidone, isopropyl myristate and other conventionally employed acceptable carriers. The pharmaceutical preparation may also contain non-toxic auxiliary substances such as emulsifying, preserving, wetting agents, bodying agents and the like, as for example, polyethylene glycols 200, 300, 400 and 600, carbowaxes 1,000, 1,500, 4,000, 6,000 and 10,000, antibacterial components such as quaternary ammonium compounds, phenylmercuric salts known to have cold sterilizing properties and which are non-injurious in use, thimerosal, methyl and propyl paraben, benzyl alcohol, phenyl ethanol, buffering ingredients such as sodium borate, sodium acetates, gluconate buffers, and other conventional ingredients such as sorbitan monolaurate, triethanolamine, oleate, polyoxyethylene sorbitan monopalmitylate, dioctyl sodium sulfosuccinate, monothioglycerol, thiosorbitol, ethylenediamine tetracetic acid, and the like. Additionally, suitable ophthalmic vehicles can be used as carrier media for the present purpose including conventional phosphate buffer vehicle systems, isotonic boric acid vehicles, isotonic sodium chloride vehicles, isotonic sodium borate

vehicles and the like. The pharmaceutical preparation may also be in the form of a microparticle formulation. The pharmaceutical preparation may also be in the form of a solid insert. For example, one may use a solid water soluble polymer as the carrier for the medicament. The polymer used to form the insert may be any water soluble non-toxic polymer, for example, cellulose derivatives such as methylcellulose, sodium carboxymethyl cellulose, (hydroxyloweralkyl cellulose), hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose; acrylates such as polyacrylic acid salts, ethylacrylates, polyactylamides; natural products such as gelatin, alginates, pectins, tragacanth, karaya, chondrus, agar, acacia; the starch derivatives such as starch acetate, hydroxymethyl starch ethers, hydroxypropyl starch, as well as other synthetic derivatives such as polyvinyl alcohol, polyvinyl pyrrolidone, polyvinyl methyl ether, polyethylene oxide, neutralized carbopol and xanthan gum, gellan gum, and mixtures of said polymer.

Suitable subjects for the administration of the formulation of the present invention include primates, man and other animals, particularly man and domesticated animals such as cats and dogs.

The pharmaceutical preparation may contain non-toxic auxiliary substances such as antibacterial components which are non-injurious in use, for example, thimerosal, benzalkonium chloride, methyl and propyl paraben, benzyldodecinium bromide, benzyl alcohol, or phenylethanol; buffering ingredients such as sodium chloride, sodium borate, sodium acetate, sodium citrate, or gluconate buffers; and other conventional ingredients such as sorbitan monolaurate, triethanolamine, polyoxyethylene sorbitan monopalmitylate, ethylenediamine tetraacetic acid, and the like.

The ophthalmic solution or suspension may be administered as often as necessary to maintain an acceptable IOP level in the eye. It is contemplated that administration to the mamalian eye will be about once or twice daily.

For topical ocular administration the novel formulations of this invention may take the form of solutions, gels, ointments, suspensions or solid inserts, formulated so that a unit dosage comprises a therapeutically effective amount of the active component or some multiple thereof in the case of a combination therapy.

The following examples given by way of illustration is demonstrative of the present invention.

Definitions of the terms used in the examples are as follows:

SM - Starting material,

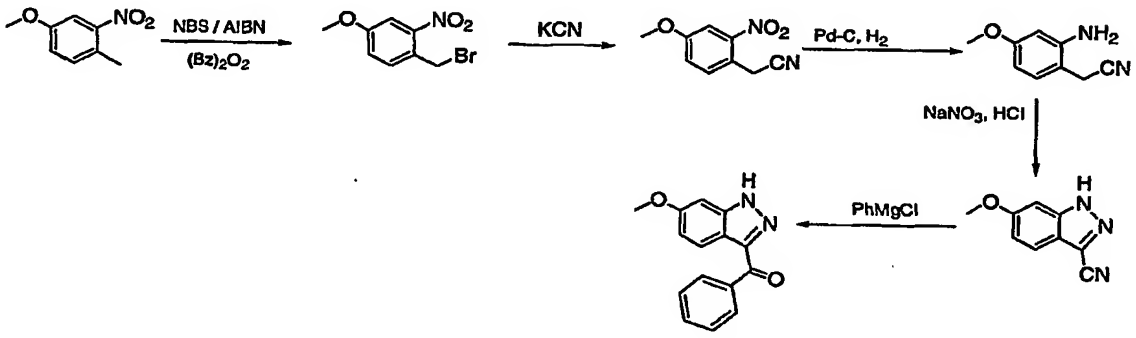
DMSO – dimethyl sulfoxide,

TLC – thin layer chromatography,

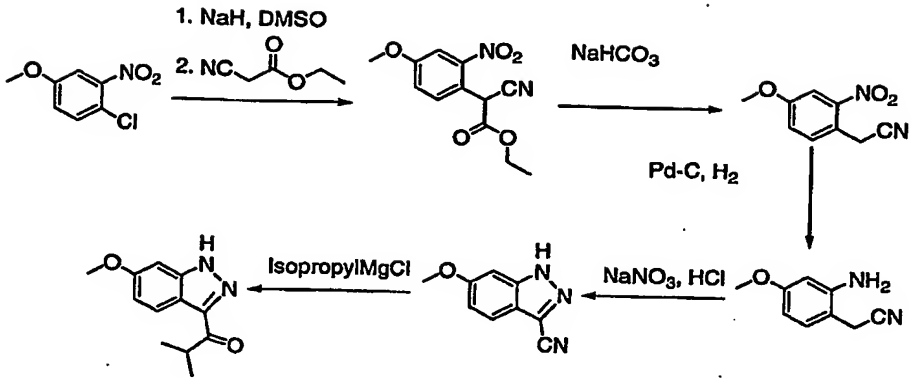
SGC – silica gel chromatography,
PhMgBr – phenylmagnesiumbromide
h = hr = hour,
THF – tetrahydrofuran,
DMF – dimethylformamide,
min – minute,
LC/MS – liquid chromatography/mass spectrometry,
HPLC – high performance liquid chromatography,
PyBOP – Benzotriazol-1-yloxytris-(dimethyl amino)phosphonium hexafluorophosphate,
equiv = eq = equivalent,
NBS – N-Bromosuccinamide and
AIBN – 2,2'-azobisisobutyronitrile.

The compounds of this invention can be made, with modification where appropriate, in accordance with Schemes 1 and/or 2. Examples 1-3 are also produced in accordance with Schemes 1 and/or 2.

Scheme 1

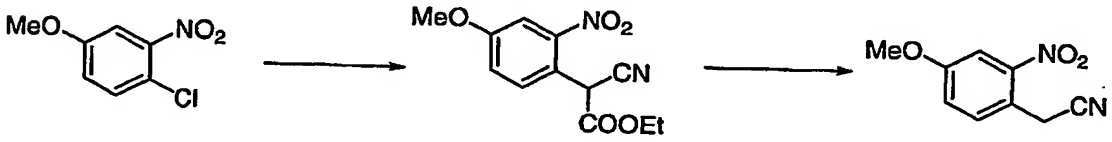


Scheme 2



In Schemes 1 and 2 nitroanisole is brominated using NBS, AIBN and benzoyl peroxide. Treatment of the bromonitroanisole with potassium cyanide yielded the cyanonitroanisole. Conversion of the nitro group to an amine is accomplished by hydrogenation. The amine is then treated with sodium nitrite and HCl to yield the indazole ring. In this reaction as soon as the diazonium is generated by nitrosation of the aniline moiety it is trapped intramolecularily by the acidic benzyl cyanide. Tautomerization of the resultant derivative gives the indazole nucleus. Treatment of the nitrile with a Gringard followed by hydrolysis of the resultant imino-magnesium complex gives the desired alkyl/aryl ketone.

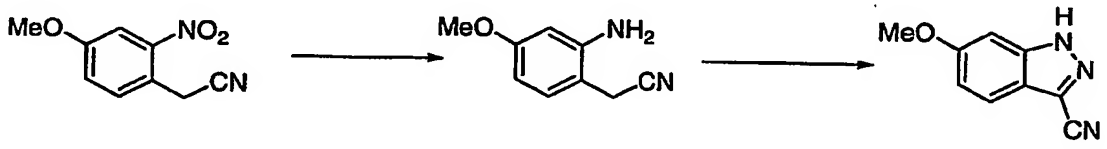
Preparative Example 1



In a 500 mL flask was charged 336 mmoles (13.44g; 60%) of NaH. Under argon 150 mL of DMSO was added, followed by dropwise addition of 32 mL of ethyl cyanoacetate (2.2 equiv.; 352 mmloes) at 5o C. After all the addition the reaction was warmed upto room temperature over 1h. 30 g of starting nitro benzene derivative was added (160 mmoles) as a powder. The reaction mixture was heated in a closed system at 90oC for 8hours. Acidification and standard work-up gave a crude oily residue which was purified over a silica-gel column to

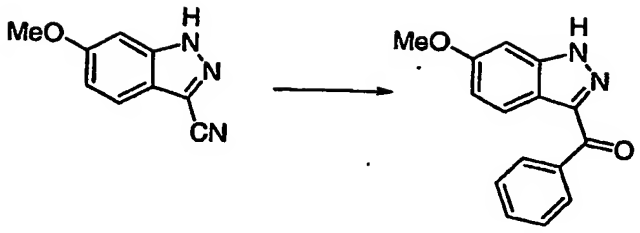
give 39 g of desired crystalline product which was decarboxylated to give the benzyl nitrile as follows. Thirty eight grams of SM obtained above was dissolved in 400 mL of 1N sodium carbonate. The homogenous solution was stirred at rt for two days. TLC analysis indicated competion of reaction. The reaction mixture was acidified and extratced with ethyl acetate (100 mL X 4). The combined organic phases was dried over sodium sulphate and concentrated and residue was subjected to SGC to give the desired product.
1H NMR CDCL3: 7.72 (1H, d, J = 3 Hz); 7.61 (1H, d, J = 8.5 Hz); 7,25 (1H, dd, J = 3 and 8.5 Hz); 4.17 (2H, s); 3.94 (3H, s). LCMS [M+H] = 193.

Preparative Example 2



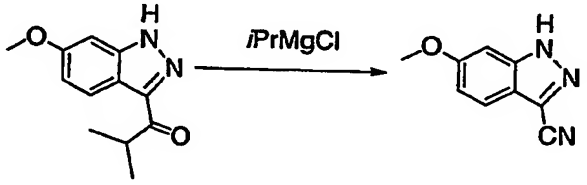
10g of benzylnitrile derivative was dissolved in THF 20 mL followed by dilution with 50 mL of methanol. The reaction mixture was taken in a pressure tube, Pd-C (10% wt/ 10 mole %) was added and the reaction mixture was hydrogenated at 40 psi. After the requisite amount of hydrogen for the reduction of the NO_2 group was consumed the reaction was stopped. TLC analysis indicated a spot to spot conversion. The reaction mixture was filtered over a pad of celite and the filtrate was concentrated to a solid and used in the next step directly. Crude aniline derivative (52 mmoles was dissloved/suspended in 2N HCl (150 mL), cooled to 5 ^oC followed by the addition of 5.4g of sodium nitrite in 10 mL of water. The reaction mixture was allowed to stir for 1h with gradual warming to room temperature. TLC analysis indicated complete consumption of SM and the formation of a new spot. The reaction mixture was extratced with ethyl acetate (100 mL X 4); organic phase was collected, dried and concentrated. The residue was purified by SGC to give desired product. LCMS [M+H] = 174

Preparative Example 3



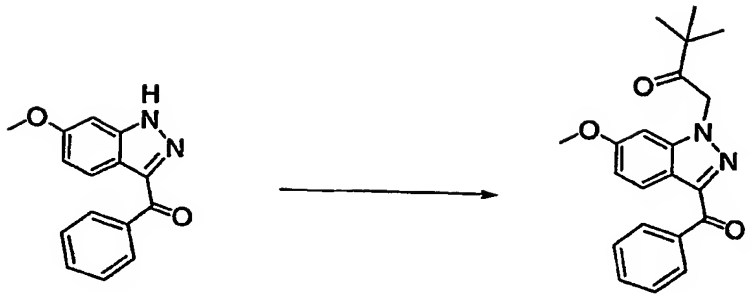
Nitrile (1.5 g) obtained from Preparative Example 2 was dissolved in 20 mL of dry THF and under argon 3 equiv. of PhMgBr (1M in THF) was added at 5°C. The reaction mixture was stirred at room temperature for 1h. The reaction was carefully quenched by addition of water and 1N HCl (15 mL). The quenched reaction mixture was stirred at room temperature for 1hour then extracted with ethyl acetate (20 mL X3); combined organic phases were dried over sodium sulfate and concentrated to a solid residue which was azeotroped with toluene three times. LCMS [M+H] = 253

Preparative Example 4



Weighed out 4.15 g of indazole and azeoptroped water with 2 toluene (100 ml) washings, pulling off toluene azeotrope by rotovap. Dried thoroughly under high vaccuum and performed argon purges. Dissolved in 40 ml dry THF and 92 ml dry ether under argon. Cooled to 5°C in ice water bath. Charged 3 eq of isopropylmagnesium chloride ((6 ml of a 2M solution in THF) and stired for 0.5 hr at room temp. Carefully charged 1N HCl (240 ml) and stired for 1 h. Monitored reaction by TLC. Extracted with EtOAc, rotovaped and produced desired product. LCMS [M+H] = 219

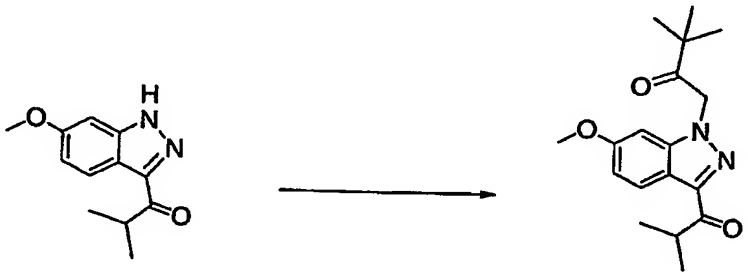
Example 1



Indazole (0.55 mmoles from Preparative Example 3) starting material obtained as above was dissolved in DMF (3 mL) followed by the addition of sodium hydride (0.88 mmoles) . The reaction was stirred at room temperature for 15 min, followed by the addition of tert-butyl bromo acetate (0.669 mmoles). The reaction was stirred at room temperature for 30 min. TLC and LC-MS analysis indicated complete consumption of starting material concurrent with the formation of a new product spot. The reaction mixture was quenched by the addition of water. Standard aqueous work-up followed by purification of crude by SGC gave the desired product as white solid.

1H NMR CDCL3: 8.3 (3H, m); 7.61 (1H, t, J = 7.5 Hz); 7.52 (2H, dd, J = 7.5 and 7.0 Hz); 7.04 (1H, dd, J = 2 and 9 Hz); 6.56 (1H, d, J = 2 Hz); 5.4 (2H, s); 3.94 (3H, s); 1.4 (9H, s). LCMS [M+H] = 351.

Example 2

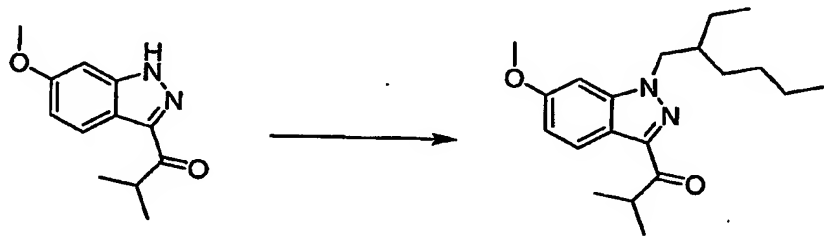


Indazole (0.60 mmoles from Preparative Example 4) starting material obtained as above was dissolved in DMF (3 mL) followed by the addition of sodium hydride (0.88 mmoles) . The reaction was stirred at room temperature for 15 min, followed by the addition of tert-butyl bromo acetate (0.669 mmoles). The reaction was stirred at room temperature for 30 min. TLC and LC-

MS analysis indicated complete consumption of starting material concurrent with the formation of a new product spot. The reaction mixture was quenched by the addition of water. Standard aqueous work-up followed by purification of crude by SGC gave the desired product as white solid.

1H NMR in CDCL: 8.22 (1H, d, J = 9 Hz); 6.97 (1H, dd, J = 2 and 9 Hz); 6.5 (1H, d J = 2 Hz); 5.4 (2H, s); 3.94 (3H, s); 2.8 (1H, m); 1.38 (9H, s); 1.27 (6H, d, J = 6.5 Hz).
LCMS = [M+H] = 317

Example 3

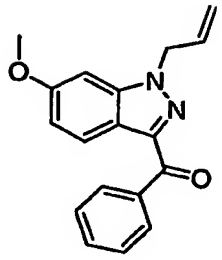


133 mg of indazole from Preparative Example 4 was dissolved in dry DMF (3 mL), followed by the addition of sodium hydride (24.3 mg, 60% oil dispersion). After stirring at room temperature for 15 min. 0.2 mL of 2-ethyl-hexyl iodide was added. The reaction mixture was allowed to stirr for an additional 10h. Upon standard aqueous work-up followed by purification by SGC the desired product was obtained.

1HNMR CDCL3: 8.22 (1H, d, J = 8.5 Hz); 7.0 (1H, dd, J = 8.5 and 2 Hz); 6.75 (1H, d, J = 2 Hz); 4.23 (2H, d, J = 7.5 Hz); 3.9 (3H, s); 2.2 (1H, m); 0.8 – 1.5 (15h, m).
LCMS [M+H] = 331

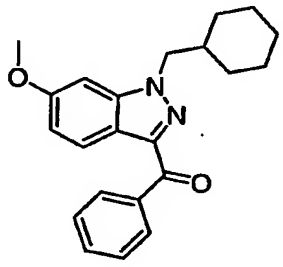
Examples 4 through 15 as shown below are made, with some modification of the desired compound of Preparative Example 3, by alkylation of the indazole as described in Example 1. Additionally, analogs of Examples 1 and 4-15 can be prepared following analogous procedures using the indazole of Preparative Example 4 or alternatively another indazole prepared following procedures described herein.

Example 4



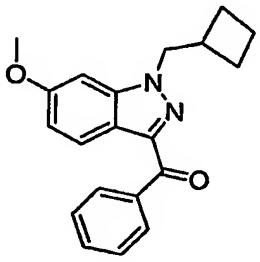
1H NMR CDCL3: 8.35 (3H, m); 7.6 (1H, t); 7.55 (2H, t); 7.1 (1H, dd, J = 8.5 and 2 Hz); 6.8 (1H, d, J = 2 Hz); 5.9 (1H, m); 5.15 (2H, m); 4.5 (2H, t); 3.9 (3H, s); 2.8 (2H, m).
LCMS [M+H] = 307

Example 5



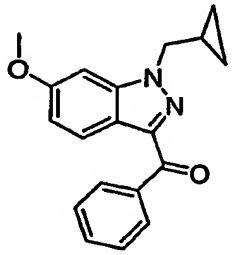
1H NMR CDCL3: 8.35 (3H, m); 7.6 (1H, t); 7.55 (2H, t); 7.1 (1H, dd, J = 8.5 and 2 Hz); 6.8 (1H, d, J = 2 Hz); 4.25 (2H, d, J = 7.5 Hz); 3.9 (3H, s); 1 – 2.2 (11H, m).
LCMS [M+H] = 349

Example 6



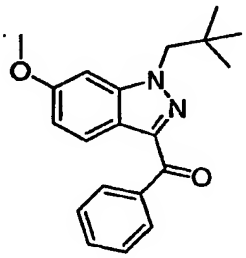
1H NMR CDCL3: 8.35 (3H, m); 7.6 (1H, t); 7.55 (2H, t); 7.1 (1H, dd, J = 8.5 and 2 Hz); 6.8 (1H, d, J = 2 Hz); 4.45 (2H, d, J = 7.5 Hz); 3.9 (3H, s); 3.0 (1H, m); 1.8 – 2.2 (6H, m).
LCMS [M+H] = 321

Example 7



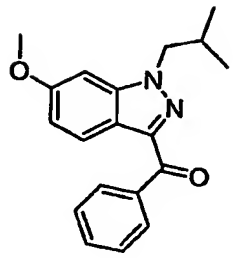
1H NMR CDCL3: 8.35 (3H, m); 7.6 (1H, t); 7.55 (2H, t); 7.1 (1H, dd, J = 8.5 and 2 Hz); 6.8 (1H, d, J = 2 Hz); 4.35 (2H, d, J = 7.5 Hz); 3.9 (3H, s); 1.4 (1H, m); 0.7 (2H, m); 0.5 (2H, m).
LCMS [M+H] = 307

Example 8



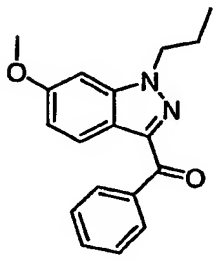
1H NMR CDCL3: 8.35 (3H, m); 7.6 (1H, t); 7.55 (2H, t); 7.1 (1H, dd, J = 8.5 and 2 Hz); 6.8 (1H, d, J = 2 Hz); 4.2 (sH, s); 3.9 (3H, s); 1.1 (9H, s).
LCMS [M+H] = 323

Example 9



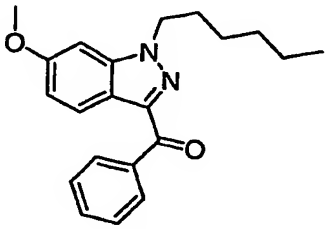
1H NMR CDCL3: 8.35 (3H, m); 7.6 (1H, t); 7.55 (2H, t); 7.1 (1H, dd, J = 8.5 and 2 Hz); 6.8 (1H, d, J = 2 Hz); 4.25 (2H, d, J = 7.5 hZ); 3.9 (3H, s); 2.6 (1H, m); 1.02 (6H, d).
LCMS [M+H] = 309

Example 10



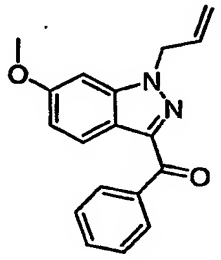
1H NMR CDCL3: 8.35 (3H, m); 7.6 (1H, t); 7.55 (2H, t); 7.1 (1H, dd, J = 8.5 and 2 Hz); 6.8 (1H, d, J = 2 Hz); 4.4 (2H, t, J = 7.5 Hz); 3.9 (3H, s); 2.o (2H, m); 1.02 (3H, t, J = 7.5 Hz).
LCMS [M+H] = 295

Example 11



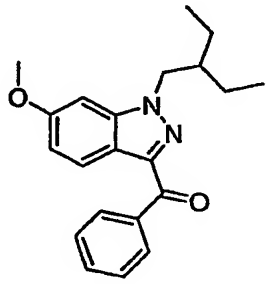
1H NMR CDCL3: 8.35 (3H, m); 7.6 (1H, t); 7.55 (2H, t); 7.1 (1H, dd, J = 8.5 and 2 Hz); 6.8 (1H, d, J = 2 Hz); 4.4 (2H, t, J = 7.5 Hz); 3.9 (3H, s); 2.0 (2H, m); 0.8 – 1.5 (5H, m).
LCMS [M+H] = 337

Example 12



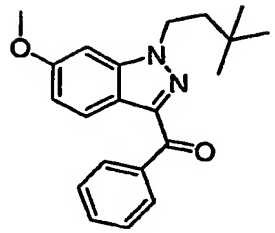
1H NMR CDCL3: 8.35 (3H, m); 7.6 (1H, t); 7.55 (2H, t); 7.1 (1H, dd, J = 8.5 and 2 Hz); 6.8 (1H, d, J = 2 Hz); 6.2 (1H, m); 5.0 – 5.4 (3H, m); 3.9 (3H, s).
LCMS [M+H] = 293

Example 13



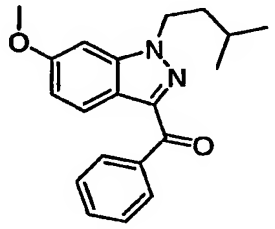
1H NMR CDCL3: 8.35 (3H, m); 7.6 (1H, t); 7.55 (2H, t); 7.1 (1H, dd, J = 8.5 and 2 Hz); 6.8 (1H, d, J = 2 Hz); 4.4 (2H, d, J = 7.5 Hz); 3.9 (3H, s); 2.1 (1H, m); 1.4 (4H, m); 1.0 (6H, t, J = 7.5 Hz).
LCMS [M+H] = 337

Example 14



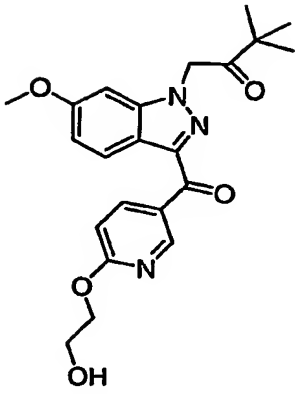
1H NMR CDCL3: 8.35 (3H, m); 7.6 (1H, t); 7.55 (2H, t); 7.1 (1H, dd, J = 8.5 and 2 Hz); 6.8 (1H, d, J = 2 Hz); 4.4 (2H, t, J = 7.5 Hz); 3.9 (3H, s); 1.9 (2H, t, J = 7.5 Hz); 1.1 (9H, s).
LCMS [M+H] = 337.

Example 15

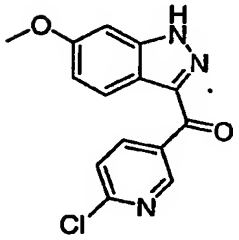


1H NMR CDCL3: 8.35 (3H, m); 7.6 (1H, t); 7.55 (2H, t); 7.1 (1H, dd, J = 8.5 and 2 Hz); 6.8 (1H, d, J = 2 Hz); 4.5 (2H, t, J = 7.5 Hz); 3.9 (3H, s); 1.9 (2H, m); 1.7 (1H, m); 1.05 (6H, d, J = 7.5 Hz).
LCMS [M+H] = 323

Example 16

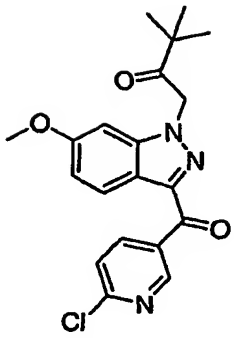


Step A:



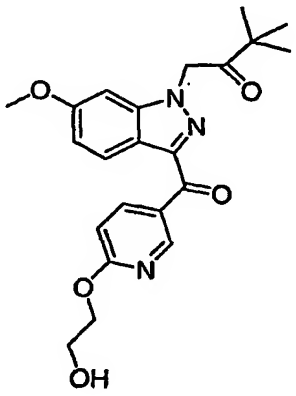
To a solution of 5-iodo-2-chloropyridine (2.56 g, 10.78 mmol) in THF (10 mL) was added *i*PrMgBr dropwise at -78 °C. The reaction stirred for 1 h before Intermediate 1 (1.71 g, 6.10 mmol) was added as a solution in THF (5 mL). After 2 h and the reaction was quenched with 1N NaOH and extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. To a solution of the crude product in toluene (50 mL) was added MnO_2 (2.173 g, 25.0 mmol) and the reaction mixture was heated to 130 °C. After 1h the reaction was complete, filtered through a celite pad, and concentrated *in vacuo*. The crude product was dissolved in THF (10 mL) and 4 mL of 1N HCl was added dropwise. The reaction stirred at RT until TLC analysis indicated completion. The reaction mixture was cooled to 0°C and the solid precipitate was collected. ^1H NMR (CD_3OD) δ : 3.900 (3H, s), 7.013 (1H, d), 7.062 (1H, s), 7.627 (1H, d), 8.672 (1H, d), 9.306 (1H, s).

Step B:



To a solution of the intermediate from Step A (1.00 g, 3.48 mmol) and Cs_2CO_3 (3.396 g, 10.45 mmol) in DMF (14 mL) was added 1-chloropinacolone (0.681 mL, 5.22 mmol). After 40 min the reaction was complete and quenched with H_2O. The reaction mixture was extracted with EtOAc and the combined organic layers were washed with H_2O, brine, dried over $MgSO_4$, and concentrated *in vacuo* to yield the desired product. ^1H NMR (CD_3OD) δ: 1.344 (9H, s), 3.888 (3H, s), 6.947 (1H, s), 7.043 (1H, d), 7.625 (1H, d), 8.221 (1H, d), 8.624 (1H, d), 9.257 (1H, d).

Step C:

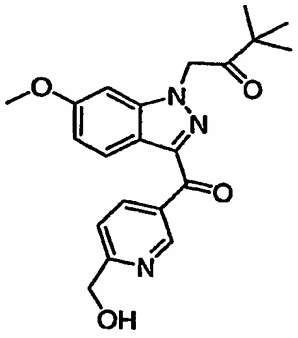


40.6 mg (1.036 mmol) of NaH (60% dispersion in mineral oil) was washed 3x with hexane and dried under nitrogen. Ethylene glycol (1mL) was added to the dry NaH and the reaction stirred for 20 min at 60 °C. To the reaction mixture was added the intermediate from Step B (100 mg, 0.259 mmol) as a solution in THF (1.5 mL). The reaction continued to stir overnight at 60 °C. Upon completion, the THF was removed *in vacuo*, diluted with EtOAc, washed with H_2O, brine,

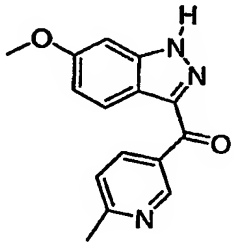
dried over $MgSO_4$, and concentrated *in vacuo*. The crude residue was purified via silica gel chromatography.

1.376 (9H, s), 3.889 (3H, s), 4.021 (2H, m), 4.608 (2H, m), 5.429 (2H, s), 6.543 (1H, s), 6.223 (1H, d), 7.054 (1H, d), 8.336 (1H, d), 8.541 (1H, d), 9.310 (1H, s).

Example 17



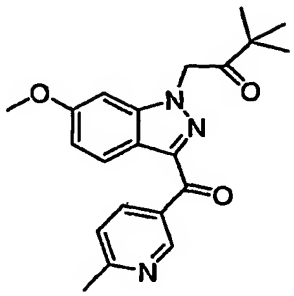
Step A:



To a solution of 5-bromo-2-methylpyridine (736 mg, 4.31 mmol) in THF (15 mL) was added *n*BuLi dropwise (2.156 mL, 5.39 mmol, 2.5 M in hexanes) at –78 °C. The reaction stirred for 1 h before Intermediate 1 (1.00 g, 3.59 mmol) was added as a solution in THF (5 mL). The starting material was consumed after 2 h and the reaction was quenched with 1N NaOH and extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. A solution of the crude product in toluene (20 mL) was added MnO_2 (0.414 g, 4.77 mmol) and the reaction mixture was heated to 130 °C. After 1h the reaction was complete, filtered through a celite pad, and concentrated *in vacuo*. The crude product was dissolved in THF and 4 mL of 1N HCl was added dropwise. After 1h reaction mixture was

cooled to 0 °C and the solid precipitate was collected. ^{1}H NMR (DMSO) δ : 2.553 (3H, s), 3.832 (3H, s), 7.000 (1H, d), 7.089 (1H, s), 7.451 (1H, d), 8.100 (1H, d), 8.430 (1H, d), 9.220 (1H, s).

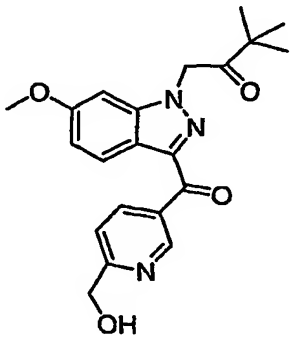
Step B:



This compound was made as described in Step B of Example 16.

^{1}H NMR ($CDCl_3$) δ : 1.38 (9H, s), 2.65 (3H, s), 3.85 (3H, s), 5.22 (2H, s), 6.56 (1H, s), 7.05 (1H, d), 7.32 (1H, d), 8.34 (1H, d), 8.45 (1H, d), 9.50 (1H, s).

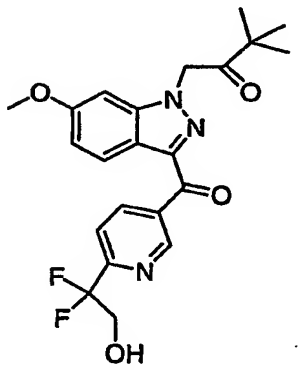
Step C:



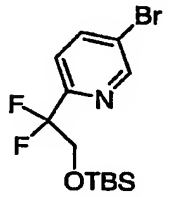
To a stirring solution of the intermediate from Step B (74 mg, 0.202 mmol) in CH_2Cl_2 was added MCPBA (67 mg, 0.303 mmol) at 0 °C. TLC indicated the reaction was complete after 1.5 h and the reaction mixture was concentrated *in vacuo*. The crude residue was dissolved in EtOAc and washed with saturated sodium bisulfite, H_2O, brine, dried over $MgSO_4$, and concentrated *in vacuo*. Purified via silica gel chromatography. The N-oxide was dissolved in CH_2Cl_2 and TFAA was added dropwise at 0 °C. After 2h the reaction was concentrated *in vacuo* and purified via silica gel chromatography.

^{1}H NMR ($CDCl_3$) δ :1.373 (9H, s), 3.898 (3H, s), 4.882 (2H, s), 5.428 (2H, s), 6.564 (1H, s), 7.066 (1H, d), 7.429 (1H, d), 8.352 (1H, d), 8.581 (1H, d), 9.541 (1H, s).

Example 18



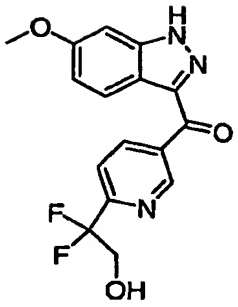
Step A:



To a solution of 2-pyridineacetic acid, 5-bromo-α,α-difluoro-, ethyl ester (13.4g; prepared according to "Ero, H.; Haneko, Y.; Sakamoto, T. *Chem Pharm. Bull.* **2000**,*48*, 982.") in ethanol was added sodium borohydride (2.3g) portion-wise at 0 °C. After stirring at 0 °C for 1 hour, the mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with 1N $NaOH_{aq}$, brine, dried ($MgSO_4$), and concentrated under reduced pressure to afford crude alcohol. The crude alcohol in methylene chloride was added imidazole (4.1g) and TBS-Cl (8.3g) at 0 °C. The mixture was stirred for 1 hour. The reaction was poured into 0.1 N HCl_{aq} extracted with methylene chloride. The organic layer was washed with brine, dried ($MgSO_4$) and evaporated. The residue was purified by silica gel (100% methylene chloride) to give desired compound as a colorless oil.

^{1}H NMR ($CDCl_3$) : δ 8.75 (1H, d); 7.95 (1H, dd); 7.57 (1H, d); 4.20 (2H, t); 0.82 (9H, s); 0.02 (6H, s).

Step B:

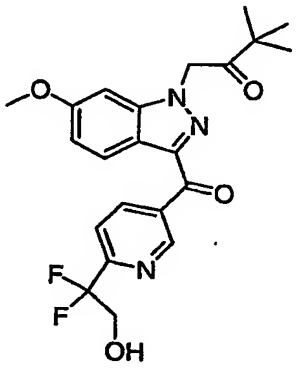


The desired compound was prepared by a procedure similar to the one described for Example 16, Step A.

^{1}H NMR (DMSO) : δ 9.35 (1H, d); 8.65 (1H, dd); 8.14 (1H, d); 7.88 (1H, d); 7.10 (1H, d); 7.03 (1H, dd); 4.05 (2H, t); 3.85 (3H, s).

LC-MS (M+H)=334.2.

Step C:

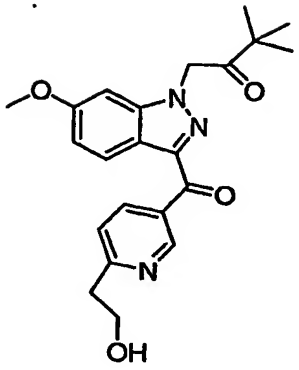


The desired compound was prepared by a procedure similar to the one described for Example 16, Step B. This compound was purified by silica gel (hexanes/ ethyl acetate=1/1) and crystalized from hexanes/ ethyl acetate.

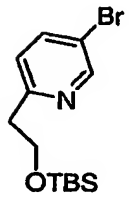
^{1}H NMR ($CHCl_3$) : δ 9.53 (1H, d); 8.71 (1H, dd); 8.35 (1H, d); 7.88 (1H, d); 7.08 (1H, dd); 6.57 (1H, d); 5.44 (2H, s); 4.32 (2H, t); 3.91 (3H, s); 1.38 (9H, s).

LC-MS (M+H)=432.3.

Example 19



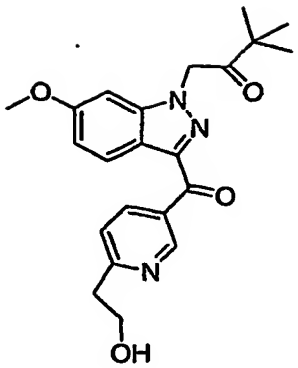
Step A:



To a solution of 2,5-dibromopyridine (2.4g) in toluene was added tributylallyltin (3.4 ml) and dichlorobis(triphenylphosphine) palladium (0.7g) under nitrogen atmosphere. The mixture was refluxed for a couple of hours and concentrated under reduced pressure. The residue was re-dissolved in "wet ether" and added DBU (3ml) slowly to give a cloudy solution. The mixture was filtered over a pad of silica gel and concentrated. The residue was dissolved in methylene chloride/methanol=1/1 solution and cooled to –78 °C. To this solution was bubbled though ozone until the reaction mixture became a blue color. The reaction was warmed to 0 °C and added sodium borohydride (0.5g) portion-wise. After stirring at 0 °C for 1 hour, the mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with 1N $NaOH_{aq}$, brine, dried ($MgSO_4$), and concentrated under reduced pressure to afford crude alcohol. The alcohol was purified by silica gel (methylene chloride/ ethyl acetate=1/1) to give desired alcohol. To a solution of alcohol in methylene chloride was added imidazole (0.4g) and TBS-Cl (0.8g) at 0 °C. The mixture was stirred for 1 hour. The reaction was poured into 0.1 N HCl_{aq} extracted with methylene chloride. The organic layer was washed with brine, dried ($MgSO_4$) and evaporated. The residue was purified by silica gel (100% methylene chloride) to give desired compound.

^1H NMR ($CDCl_3$) : δ 8.61 (1H, d); 7.73 (1H, dd); 7.14 (1H, d); 3.97 (2H, t); 2.96 (2H, t); 0.86 (9H, s); -0.02 (6H, s).

Step B:



The desired compound was prepared by a procedure similar to the one described for Example 16, Steps A and B. This compound was purified by silica gel (hexanes/ ethyl acetate=1/3).
^{1}H NMR ($CHCl_3$) : δ 9.53 (1H, d); 8.54 (1H, dd); 8.35 (1H, d); 7.37 (1H, d); 7.07 (1H, dd); 6.56 (1H, d); 5.45 (2H, s); 4.11 (2H, t); 3.90 (3H, s); 3.18 (2H, t); 1.38 (9H, s).
LC-MS (M+H)=396.2.

FUNCTIONAL ASSAYS

A. Maxi-K Channel

The identification of inhibitors of the Maxi-K channel can be accomplished using Aurora Biosciences technology, and is based on the ability of expressed Maxi-K channels to set cellular resting potential after transient transfection of both α and β subunits of the channel in TsA-201 cells. In the absence of inhibitors, cells display a hyperpolarized membrane potential, negative inside, close to E_K (-80 mV) which is a consequence of the activity of the Maxi-K channel. Blockade of the Maxi-K channel will cause cell depolarization. Changes in membrane potential can be determined with voltage-sensitive fluorescence resonance energy transfer (FRET) dye pairs that use two components, a donor coumarin (CC_2DMPE) and an acceptor oxanol ($DiSBAC_2(3)$). Oxanol is a lipophilic anion and distributes across the membrane according to membrane potential. Under normal conditions, when the inside of the cell is negative with respect to the outside, oxanol is accumulated at the outer leaflet of the membrane and excitation of coumarin will cause FRET to occur. Conditions that lead to membrane depolarization will cause the oxanol to redistribute to the inside of the cell, and, as a consequence, to a decrease in FRET. Thus, the ratio change (donor/acceptor) increases after membrane depolarization.

Transient transfection of the Maxi-K channel in TsA-201 cells can be carried out as previously described (Hanner et al. (1998) J. Biol. Chem. 273, 16289-16296) using FUGENE6™ as the transfection reagent. Twenty four hours after transfection, cells are collected in Ca^{2+}-Mg^{2+}-free Dulbecco's phosphate-buffered saline (D-PBS), subjected to centrifugation, plated onto 96-well poly-d-lysine coated plates at a density of 60,000 cells/well, and incubated overnight. The cells are then washed 1x with D-PBS, and loaded with 100 µl of 4 µM CC_2DMPE-0.02% pluronic-127 in D-PBS. Cells are incubated at room temperature for 30 min in the dark. Afterwards, cells are washed 2x with D-PBS and loaded with 100 µl of 6 µM DiSBAC$_2$(3) in (mM): 140 NaCl, 0.1 KCl, 2 $CaCl_2$, 1 $MgCl_2$, 20 Hepes-NaOH, pH 7.4, 10 glucose. Test compounds are diluted into this solution, and added at the same time. Cells are incubated at room temperature for 30 min in the dark.

Plates are loaded into a voltage/ion probe reader (VIPR) instrument, and the fluorescence emission of both CC_2DMPE and DiSBAC$_2$(3) are recorded for 10 sec. At this point, 100 µl of high-potassium solution (mM): 140 KCl, 2 $CaCl_2$, 1 $MgCl_2$, 20 Hepes-KOH, pH 7.4, 10 glucose are added and the fluorescence emission of both dyes recorded for an additional 10 sec. The ratio CC_2DMPE/DiSBAC$_2$(3), before addition of high-potassium solution equals 1. In the absence of any inhibitor, the ratio after addition of high-potassium solution varies between 1.65-2.0. When the Maxi-K channel has been completely inhibited by either a known standard or test compound, this ratio remains at 1. It is possible, therefore, to titrate the activity of a Maxi-K channel inhibitor by monitoring the concentration-dependent change in the fluorescence ratio.

The compounds of this invention were found to cause concentration-dependent inhibition of the fluorescence ratio with IC_{50}'s in the range of about 1nM to about 20 µM, more preferably from about 10 nM to about 500 nM.

B. Electrophysiological assays of compound effects on high-conductance calcium-activated potassium channels

Human non-pigmented ciliary epithelial cells

The activity of high-conductance calcium-activated potassium (maxi-K) channels in human non-pigmented ciliary epithelial cells was determined using electrophysiological methods. Currents through maxi-K channels were recorded in the inside-out configuration of the patch clamp technique, where the pipette solution faces the extracellular side of the channel and the bath solution faces the intracellular side. Excised patches contained one to about fifty maxi-K channels. Maxi-K channels were identified by their large single channel conductance (250-

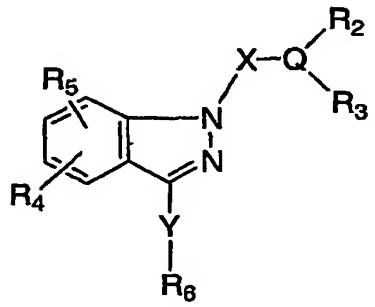
300 pS), and by sensitivity of channel gating to membrane potential and intracellular calcium concentration. Membrane currents were recorded using standard electrophysiological techniques. Glass pipettes (Garner 7052) were pulled in two stages with a Kopf puller (model 750), and electrode resistance was 1-3 megohms when filled with saline. Membrane currents were recorded with EPC9 (HEKA Instruments) or Axopatch 1D (Axon Instruments) amplifiers, and digital conversion was done with ITC-16 interfaces (Instrutech Corp). Pipettes were filled with (mM); 150 KCl, 10 Hepes, 1 $MgCl_2$, 0.01 $CaCl_2$, 3.65 KOH, pH 7.20. The bath (intracellular) solution was identical, except, in some cases, calcium was removed, 1 mM EGTA was added and 20 mM KCl was replaced with 20 mM KF to eliminate calcium to test for calcium sensitivity of channel gating. Drugs were applied to the intracellular side of the channel by bath perfusion.

Human non-pigmented ciliary epithelial cells were grown in tissue culture as described (Martin-Vasallo, P., Ghosh, S., and Coca-Prados, M., 1989, J. Cell. Physiol. 141, 243-252), and plated onto glass cover slips prior to use. High resistance seals (>1 Gohm) were formed between the pipette and cell surface, and inside out patches were excised. Maxi-K channels in the patch were identified by their gating properties; channel open probability increased in response to membrane depolarization and elevated intracellular calcium. In patches used for pharmacological analysis, removing intracellular calcium eliminated voltage-gated currents. Maxi-K currents were measured after depolarizing voltage steps or ramps that caused channel opening.

The compounds of this invention were applied to the intracellular side of the channel in appropriate concentrations (0.001 to 10 μM). The compounds reduced channel open probability, and this effect was reversed upon washout of compounds from the experimental chamber. The IC50 for block of maxi-K channels under these conditions for the compounds of this invention ranged from about 0.5 nM to about 1 μM.

WHAT IS CLAIMED IS:

1. A compound of the structural formula I:



Formula I

or a pharmaceutically acceptable salt, *in vivo* hydrolysable ester, enantiomer, diastereomer or mixture thereof:

wherein,

R represents hydrogen, or C_{1-6} alkyl;

X represents $-(CHR_7)_p-$, $-(CHR_7)_pCO-$;

Y represents $-CO(CH_2)_n-$, CH_2, or $-CH(OR)-$;

Q represents CR_Y;

R_Y represents H, or C_{1-6} alkyl;

R_w represents H, C_{1-6} alkyl, $-C(O)C_{1-6}$ alkyl, $-C(O)OC_{1-6}$ alkyl, $-SO_2N(R)_2$, $-SO_2C_{1-6}$ alkyl, $-SO_2C_{6-10}$ aryl, NO_2, CN or $-C(O)N(R)_2$;

R_2 represents hydrogen, C_{1-10} alkyl, OH, C_{2-6} alkenyl, C_{1-6} alkylSR, $-(CH_2)_nO(CH_2)_mOR$, $-(CH_2)_nC_{1-6}$ alkoxy, $-(CH_2)_nC_{3-8}$ cycloalkyl, $-(CH_2)_nC_{3-10}$ heterocyclyl, $-N(R)_2$, $-COOR$, or $-(CH_2)_nC_{6-10}$ aryl, said alkyl, heterocyclyl, or aryl optionally substituted with 1-3 groups selected from R^a;

R_3 represents hydrogen, C_{1-10} alkyl, $-(CH_2)_nC_{3-8}$ cycloalkyl, $-(CH_2)_nC_{3-10}$ heterocyclyl, $-(CH_2)_nCOOR$, $-(CH_2)_nC_{6-10}$ aryl, $-(CH_2)_nNHR_8$, $-(CH_2)_nN(R)_2$, $-(CH_2)_nN(R_8)_2$, $-(CH_2)_nNHCOOR$, $-(CH_2)_nN(R_8)CO_2R$, $-(CH_2)_nN(R_8)COR$, $-(CH_2)_nNHCOR$, $-(CH_2)_nCONH(R_8)$, aryl, $-(CH_2)_nC_{1-6}$ alkoxy, CF_3, $-(CH_2)_nSO_2R$, $-(CH_2)_nSO_2N(R)_2$, $-(CH_2)_nCON(R)_2$, $-(CH_2)_nCONHC(R)_3$, $-(CH_2)_nCONHC(R)_2CO_2R$, $-(CH_2)_nCOR_8$, nitro, cyano or halogen, said alkyl, alkoxy, heterocyclyl, or aryl optionally substituted with 1-3 groups of R^a;

or, R_2 and R_3 taken together with the intervening Q form a 3-10 membered carbocyclic or heterocyclic carbon ring optionally interrupted by 1-2 atoms of O, S, C(O) or NR, and optionally having 1-4 double bonds, and optionally substituted by 1-3 groups selected from R^a;

R_4 and R_5 independently represent hydrogen, C_{1-6} alkoxy, OH, C_{1-6} alkyl, COOR, SO_3H, $-O(CH_2)_nN(R)_2$, $-O(CH_2)_nCO_2R$, $-OPO(OH)_2$, CF_3, OCF_3 $-N(R)_2$, nitro, cyano, C_{1-6} alkylamino, or halogen; and

R_6 represents hydrogen, C_{1-10} alkyl, $-(CH_2)_nC_{6-10}$ aryl, NR_cR_d, $-NR(CH_2)_nC_{6-10}$ aryl, $-N((CH_2)_nC_{6-10}$ aryl$)_2$, $-(CH_2)_nC_{3-10}$ heterocyclyl, $-NR(CH_2)_nC_{3-10}$ heterocyclyl, $-N((CH_2)_nC_{3-10}$ heterocyclyl$)_2$ (C_{6-10} aryl)O-, $-(CH_2)_nC_{3-8}$ cycloalkyl, -COOR, $-C(O)CO_2R$, said aryl, heterocyclyl and alkyl optionally substituted with 1-3 groups selected from R^a;

R_c and R_d independently represent H, C1-6 alkyl, C_{2-6} alkenyl, C_{1-6} alkylSR, $-(CH_2)_nO(CH_2)_mOR$, $-(CH_2)_nC_{1-6}$ alkoxy, or $-(CH_2)_nC_{3-8}$ cycloalkyl;

or R_c and R_d taken together with the intervening N atom form a 4-10 membered heterocyclic carbon ring optionally interrupted by 1-2 atoms of O, S, C(O) or NR, and optionally having 1-4 double bonds, and optionally substituted by 1-3 groups selected from R^a;

R_7 represents hydrogen, C_{1-6} alkyl, $-(CH_2)_nCOOR$ or $-(CH_2)_nN(R)_2$,

R_8 represents $-(CH_2)_nC_{3-8}$ cycloalkyl, $-(CH_2)_n$ 3-10 heterocyclyl, C_{1-6} alkoxy or $-(CH_2)_nC_{5-10}$ heteroaryl, $-(CH_2)_nC_{6-10}$ aryl said heterocyclyl, aryl or heteroaryl optionally substituted with 1-3 groups selected from R^a;

R^a represents F, Cl, Br, I, CF_3, $N(R)_2$, NO_2, CN, $-COR_8$, $-CONHR_8$, $-CON(R_8)_2$, $-O(CH_2)_nCOOR$, $-NH(CH_2)_nOR$, -COOR, $-OCF_3$, CF_2CH_2OR, -NHCOR, $-SO_2R$, $-SO_2NR_2$, -SR, (C_1-C_6 alkyl)O-, $-(CH_2)_nO(CH_2)_mOR$, $-(CH_2)_nC_{1-6}$ alkoxy, (aryl)O-, $-(CH_2)_nOH$, (C_1-C_6 alkyl)$S(O)_m$-, H_2N-C(NH)-, (C_1-C_6 alkyl)C(O)-, (C_1-C_6 alkyl)OC(O)NH-, -(C_1-C_6 alkyl)$NR_w(CH_2)_nC_{3-10}$ heterocyclyl-R_w, -(C_1-C_6 alkyl)$O(CH_2)_nC_{3-10}$ heterocyclyl-R_w, -(C_1-C_6 alkyl)$S(CH_2)_nC_{3-10}$ heterocyclyl-R_w, -(C_1-C_6 alkyl)-C_{3-10} heterocyclyl-R_w, $-(CH_2)_n$-Z^1-$C(=Z^2)N(R)_2$, -(C_{2-6} alkenyl)$NR_w(CH_2)_nC_{3-10}$ heterocyclyl-R_w, -(C_{2-6} alkenyl)$O(CH_2)_nC_{3-10}$ heterocyclyl-R_w, -(C_{2-6} alkenyl)$S(CH_2)_nC_{3-10}$ heterocyclyl-R_w, -(C_{2-6} alkenyl)-C_{3-10} heterocyclyl-R_w, -(C_{2-6} alkenyl)-Z^1-$C(=Z^2)N(R)_2$, $-(CH_2)_nSO_2R$, $-(CH_2)_nSO_3H$, -$(CH_2)_nPO(OR)_2$, C_{3-10}cycloalkyl, C_{6-10} aryl, C_{3-10} heterocyclyl, C_{2-6} alkenyl, and C_1-C_{10} alkyl, said alkyl, alkenyl, alkoxy, heterocyclyl and aryl optionally substituted with 1-3 groups selected from C_1-C_6 alkyl, CN, NO_2, OH, $CON(R)_2$ and COOR;

Z^1 and Z^2 independently represents NR_w, O, CH_2, or S;

m is 0-3;
n is 0-3; and
p is 0-3.

2. A compound of the structural formula I wherein p is 1-3.

3. A compound according to claim 1 wherein Y is -$CO(CH_2)_n$.

4. A compound according to claim 1 wherein Y is CH(OR).

5. A compound according to claim 2 wherein R_6 is $(CH_2)_nC_{6-10}$ aryl, $(CH_2)_nC_{5-10}$ heteroaryl, $(CH_2)_nC_{3-10}$ heterocyclyl, NR_cR_d or $(CH_2)_nC_{3-8}$ cycloalkyl, said aryl, heteroaryl, heterocyclyl and alkyl optionally substituted with 1 to 3 groups of R^a.

6. A compound according to claim 5 wherein R_7 is hydrogen or C_{1-6} alkyl.

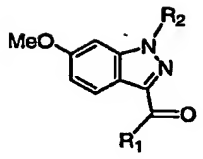
7. A compound according to claim 1 wherein Y is -$CO(CH_2)_n$, n is 0, R_2 is C_{1-10} alkyl or C_{1-6} alkylOH and R_3 is C_{1-10} alkyl or $(CH_2)_nC_{3-10}$ heterocyclyl, said heterocyclyl and alkyl optionally substituted with 1 to 3 groups of R^a.

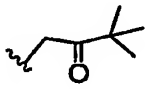
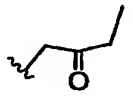
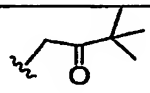
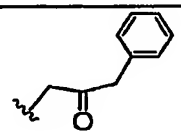
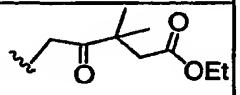
8. A compound according to claim 1 wherein X is –$(CHR_7)_p$-, p is 1-3.

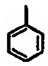
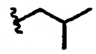
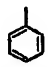
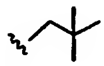
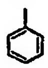
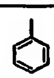
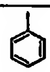
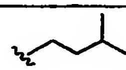
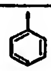
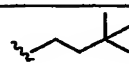
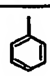
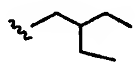
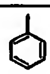
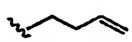
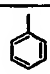
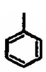
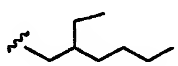
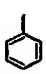
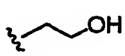
9. A compound according to claim 1 X is –$(CHR_7)_pCO$-, p is 1-3 and all other variables are as originally described.

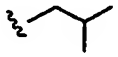
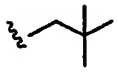
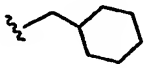
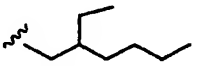
10. A compound which is:

Table 1



R1	R2
	
	
	
	
	
	

R1	R2
	
	
	
	
	
	
	
	
	
	
	
	

R1	R2
	
	
	
	
	

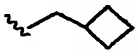
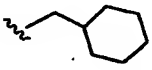
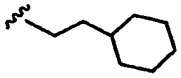
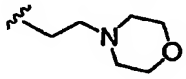
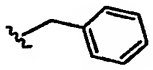
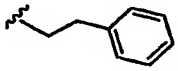
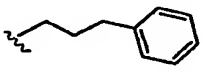
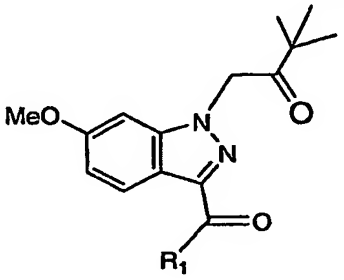
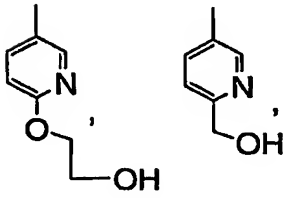
R1	R2
	
	
	
	
	
	
	
	

Table 2



wherein R_1 is



;

or a pharmaceutically acceptable salt, *in vivo* hydrolysable ester, enantiomer, diastereomer or mixture thereof.

11. A method for treating ocular hypertension or glaucoma comprising administration to a patient in need of such treatment a therapeutically effective amount of a compound of structural formula I.

12. A method for treating macular edema, macular degeneration, increasing retinal and optic nerve head blood velocity, increasing retinal and optic nerve oxygen tension, and/or a neuroprotective effect comprising administration to a patient in need of such treatment a pharmaceutically effective amount of a compound of claim 1; or a pharmaceutically acceptable salt, enantiomer, diastereomer or mixture thereof.

13. A method of preventing repolarization or hyperpolarization of a mammalian cell wherein the cell contains a potassium channel comprising the administration to a mammal, including a human, in need thereof, of a pharmacologically effective amount of a compound according to claim 1, or a pharmaceutically acceptable salt, enantiomer, diastereomer or mixture thereof.

14. A method of treating Alzheimer's Disease, depression, cognitive disorders, and/or arrhythmia disorders in a patient in need thereof comprising administering a pharmaceutically effective amount of a compound according to Claim 1, or a pharmaceutically acceptable salt, enantiomer, diastereomer or mixture thereof.

15. A method of treating diabetes in a patient in need thereof comprising administering a pharmaceutically effective amount of a compound according to claim 1, or a pharmaceutically acceptable salt, enantiomer, diastereomer or mixture thereof.

16. A composition comprising a compound of formula I and a pharmaceutically acceptable carrier.

17. The composition according to Claim 16 wherein the compound of formula I is applied as a topical formulation and said topical formulation is administered as a solution or suspension.

18. A composition according to claim 16 wherein an active ingredient belonging to the group consisting of: β-adrenergic blocking agent, parasympathomimetic agent, carbonic anhydrase inhibitor, EP4 agonist, and a prostaglandin or a prostaglandin derivative is optionally added.

19. A composition according to claim 18 wherein the β-adrenergic blocking agent is timolol; the parasympathomimetic agent is pilocarpine; the carbonic anhydrase inhibitor is dorzolamide, acetazolamide, metazolamide or brinzolamide; the prostaglandin is latanoprost or rescula, and the prostaglandin derivative is a hypotensive lipid derived from PGF2α prostaglandins.

20. A composition according to claim 16 in which the topical formulation optionally contains xanthan gum or gellan gum.

TITLE OF THE INVENTION

OPHTHALMIC COMPOSITIONS FOR TREATING OCULAR HYPERTENSION

ABSTRACT OF THE INVENTION

This invention relates to potent potassium channel blocker compounds of Formula I or a formulation thereof for the treatment of glaucoma and other conditions which leads to elevated intraoccular pressure in the eye of a patient. This invention also relates to the use of such compounds to provide a neuroprotective effect to the eye of mammalian species, particularly humans.

PATENT APPLICATION SERIAL NO. _____

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE
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